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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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Additional inventors are being named on the 1 *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

A NOVEL PROCESS FOR THE PREPARATION OF (+/-)-1-(3-DIMETHYLAMINOPROPYL)-1-(4-FLOUROPHENYL)-1,3-DIHYDROBENZOFURAN-5-CARBONITRILE (ESCITALOPRAM) AND PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

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ENCLOSED APPLICATION PARTS *(check all that apply)*

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☐ CD(s), Number
☐ Drawing(s) *Number of Sheets*
☑ Other (specify) Claims - 4 Pages
☐ Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant claims small entity status. See 37 CFR 1.27.
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[Page 1 of 2]

Respectfully submitted,

SIGNATURE

TYPED or PRINTED NAME Edward D. Pergament

Date August 4, 2004

REGISTRATION NO. 43, 346 *(if appropriate)*

Docket Number: BULK 3.8-086

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Additional Page

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Docket Number BULK 3.8-086

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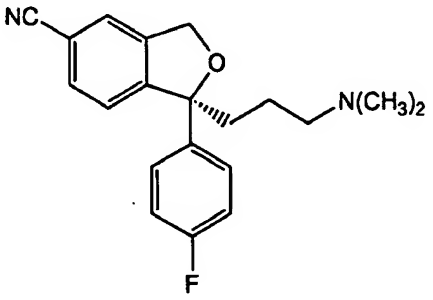
Number 1 of 1

A NOVEL PROCESS FOR THE PREPARATION OF (+)-1-(3-DIMETHYLAMINOPROPYL)-1-(4-FLOUROPHENYL)-1,3-DIHYDROBENZOFURAN-5-CARBONITRILE (ESCITALOPRAM) AND PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

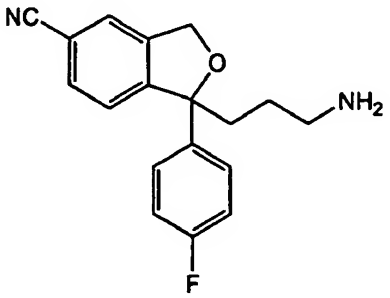
FIELD OF INVENTION:

The present invention relates to a novel process for the preparation of escitalopram, which is chemically known as (+)-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3–dihydroisobenzofuran–5–carbonitrile represented by Formula- (I)



Formula-I

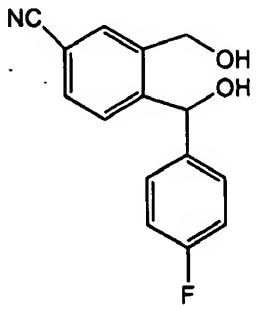
In particular, the process for the preparation of escitalopram involves a process for the preparation of didesmethyl citalopram of Formula-II, which is a useful intermediate in the preparation of escitalopram of Formula (I) and relates to a dynamic resolution of Formula (II) followed by methylation to get the escitalopram of Formula (I)



Formula-II

BACKGROUND OF INVENTION:

Escitalopram was first disclosed in US patent No 4,943,590 corresponding to EP-B1-347066. This patent describes two processes for the preparation of Escitalopram (S-enantiomer of citalopram). Both the processes utilize the racemic diol having the formula (III) as a starting material

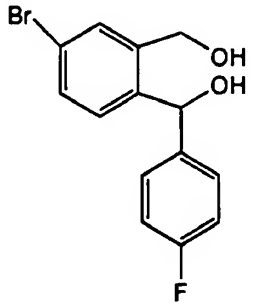


Formula - III

According to the first process, the diol of the formula (III) is reacted with an enantiomerically pure acid derivative, such as (+) or (-)-∝-metonym-∝-triflouromethyl-phenylacetyl chloride to form a mixture of diastereomeric esters, which are separated by HPLC or fractional crystallization, where upon the ester with the correct stereochemistry, is converted into escitalopram by cyclization. According to the second process, the diol of formula (III) is separated by treating with an enantiomerically pure acid such as (+)-di-*p*-tolulyltartaric acid followed by separating the required isomer by crystallization. Which upon cyclization yields escitalopram of Formula (I). Both routes found to be economically and environmentally infeasible due to their low yields.

WO03/006449 discloses a process for the preparation of escitalopram of Formula (I), which involves chromatographic separation of the enantiomers of citalopram and intermediate using a chiral stationary phase, which is industrially not feasible and not economic.

WO 03/087081 describes a process for the preparation of escitalopram via the (4-bromo-2- (hydroxymethyl) phenyl)-(4-flouro phenyl) methanol of Formula (IV), in which the racemic diol is converted to an enantiomerically enriched form by first converting the diol into monoester intermediate and then reacting monoester intermediate with an optically active acid to form a diastereomeric salt. The salt is then crystallized to obtain enantiomerically enriched S-isomer whereupon the monoester intermediate is further converted to escitalopram through suitable chemical conversions. The major drawbacks of the described process are low yields and usage of hazardous materials like copper cyanide and lengthy process of production



Formula (IV)

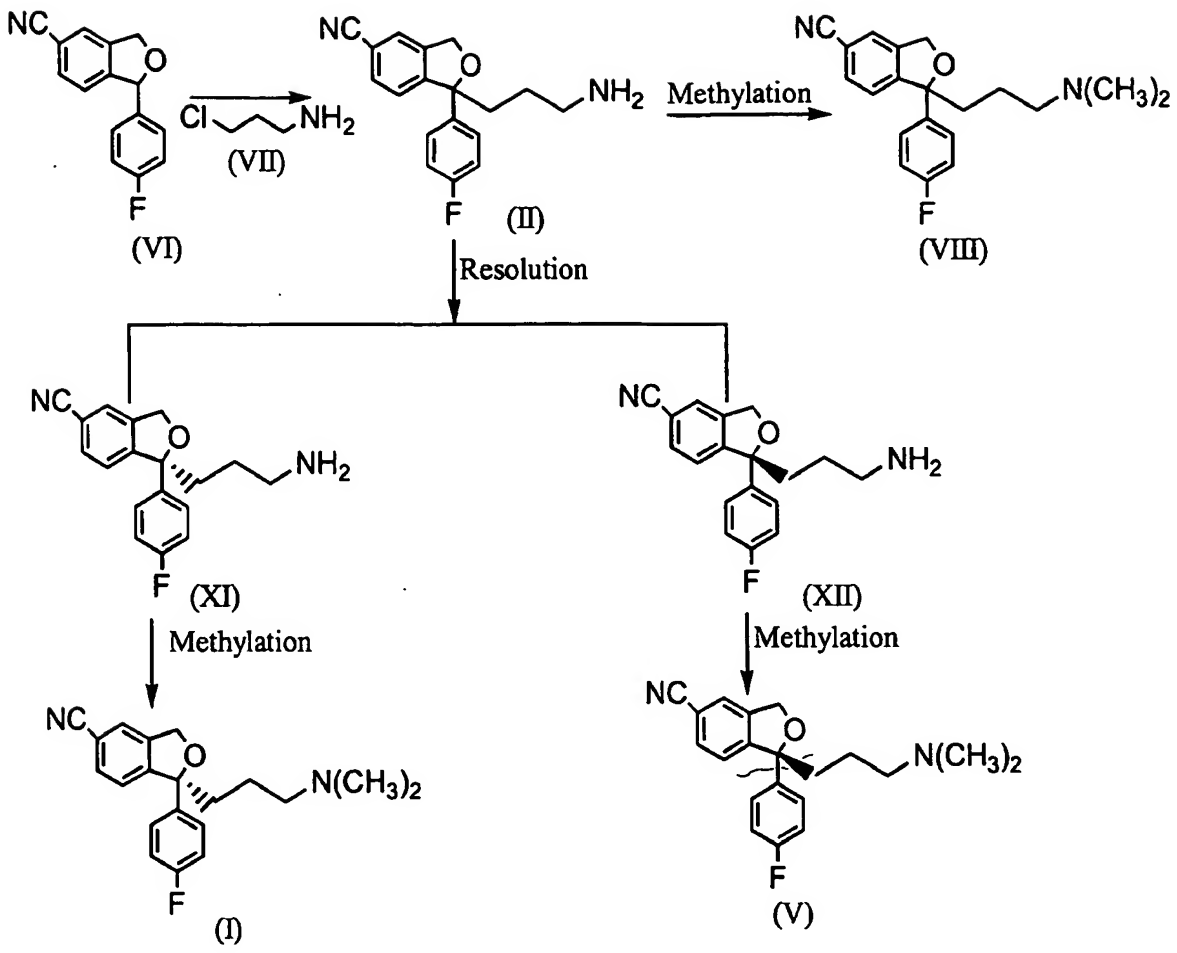
WO 03/051861 A1 describes the separation of racemic Br-citalopram to the corresponding S-Br-citalopram by fractional crystallization of diastereomeric salt of Br-citalopram and followed by hydrolysis and cyanation to get the Escitalopram. The major draw back of this process is the use of copper cyanide in presence of palladium or nickel catalyst for the conversion of bromo to cyano group, which is industrially not feasible and safe to handle.

This patent also describes the separation of bromodiol intermediate by chromatography using chiral stationary phase, which is industrially not feasible to practice at the plant level, which involves the hazardous chemical for the conversion of bromo to cyano group as described above.

With this background, we felt a need for cost effective, safe and industrially feasible route to synthesize the Escitalopram of formula-I and invention made towards this goal is described here.

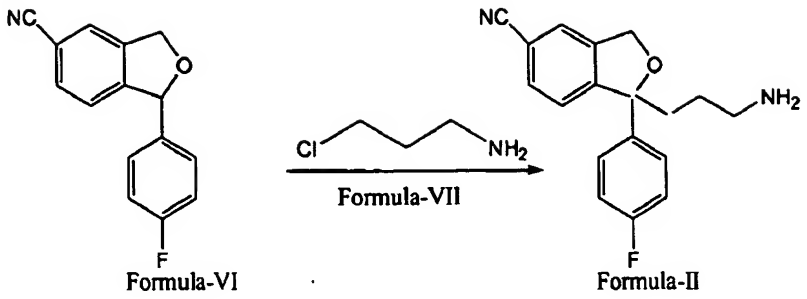
SUMMARY OF INVENTION:

One embodiment of the present invention provides a novel process for the production of (+)-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3–dihydroisobenzofuran–5–carbonitrile of Formula (I) which involves condensation of isobenzofuran of Formula (VI) with chloropropyl amine of Formula (VII) to afford a compound of Formula (II), which is further subjected to resolution followed by methylation to afford compound of Formula-I as mentioned in Scheme -I.



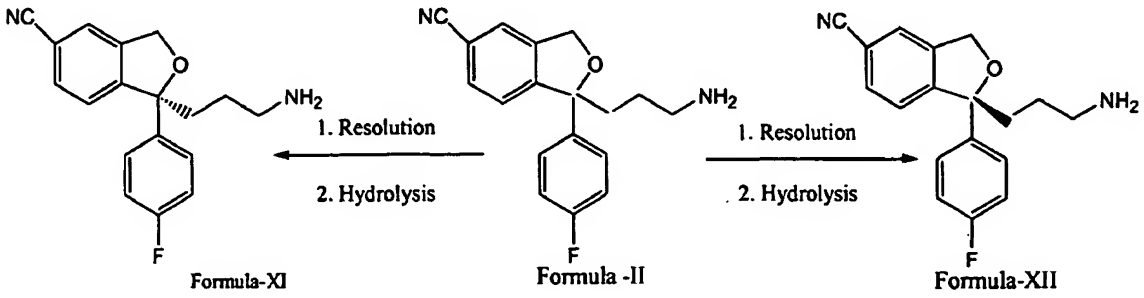
Scheme-I

Another embodiment of the present invention provides a novel process for the production of racemic 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile of Formula (II) by condensation of isobenzofuran of Formula (VI) with chloropropyl amine of Formula (VII) in a good yield and purity with industrially feasible, cost effective and safe manner as described here in Scheme-II.



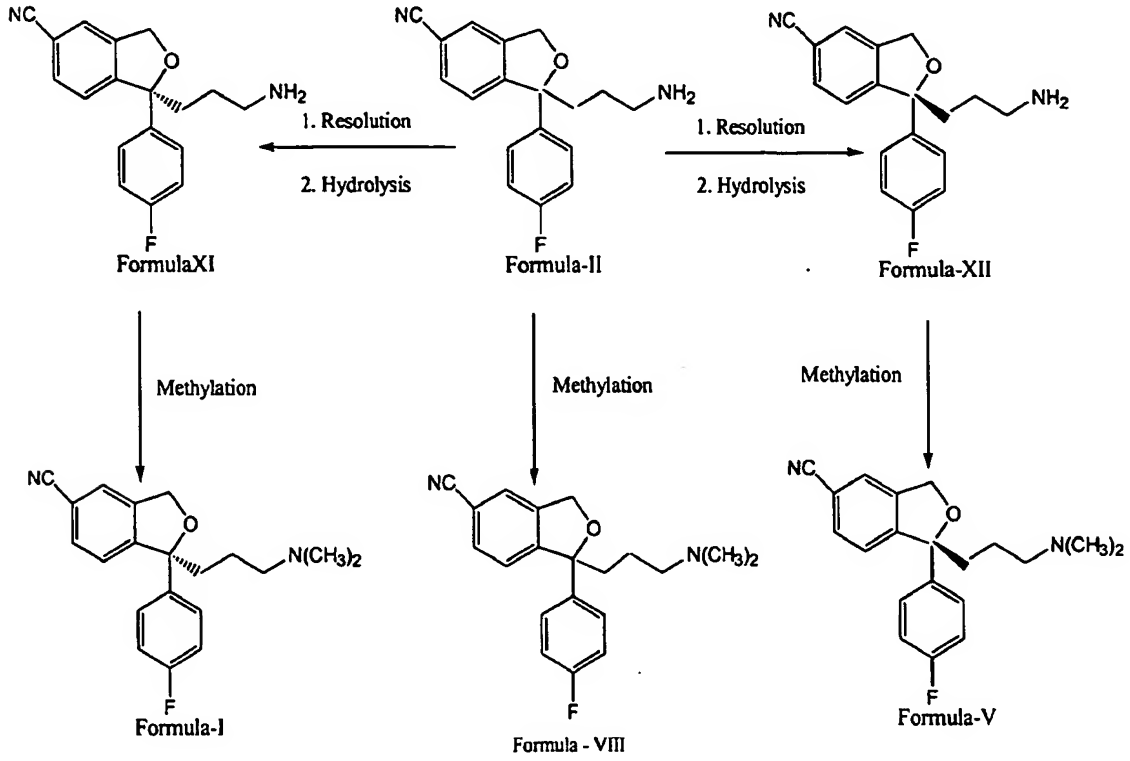
Scheme-II

Yet, another embodiment of the present invention provides a novel process for the preparation of Escitalopram of Formula (I) through the resolution of the racemic 1-(3-amino propyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile of Formula (II) to its corresponding (+)-1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile of Formula (XI) and (-)-1-(3-amino propyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile of Formula (XII) through the dynamic diastereomeric salt formation of the amine of the Formula (II) with chiral acids followed by their hydrolysis as shown in the below Scheme-III



Scheme-III

Another embodiment of the present invention also provides a process for the preparation of S-citalopram of Formula-I and R-citalopram of Formula-V by methylation of the compounds of Formula (XI) and Formula (XII) respectively as mentioned in Scheme-IV.



Scheme-IV

Another embodiment of the present invention also provides a process for the preparation of citalopram of Formula –(VIII) by methylation of compound Formula –(II) in a high yield and purity as shown in Scheme – IV.

Escitalopram can also be prepared from citalopram by diastereomeric salt formation followed by separation and hydrolysis.

Another embodiment of the present invention also relates to a novel process for the preparation of Escitalopram and /or its any salts from racemic citalopram base or its salts. The process for the preparation of Escitalopram and its pharmaceutically acceptable salts of present

invention comprises reaction of racemic citalopram (VIII) with an enantiomerically enriched acid HY*, where Y* is chiral group to form diastereomeric salt of (VIII) having Y* as counter ion, which was crystallized to separate the required salt of escitalopram which on further hydrolysis afford the Escitalopram of Formula (I).

DETAILED DESCRIPTION OF INVENTION:

According to one embodiment of the present invention, the process for the preparation of (+) 1-[3–(N, N'-dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro–5–isobenzo furancarbonitrile (S-citalopram) of the Formula–I comprising the alkylation of 5-cyano-1-(4-fluro phenyl)-1,3-dihydro isobenzofuran of Formula-VI with a compound of formula-VII in a suitable base and solvent as described, to afford racemic 1-(3-amino propyl)-1-(4-flouro phenyl)-1,3 dihydro-5-isobenzofurancarbonitrileof Formula-II. Which is further subjected to resolution with a suitable chiral acid in a suitable solvent system to obtain diastereomeric salt of the amine of Formula (II). Hydrolysis of the obtained diastereomeric salts followed by methylation of S- amine of the compound of Formula (XI) or optionally Formula (XII) to afford S-citalopram of Formula (I) or R-citalopram of Formula (V).

Didesmethylcitalopram of Formula-II can be prepared by

(i) heating a solution of a base selected form, LDA (lithium diisopropyl amine), NaH, n-BuLi, and metal oxides; such as NaOMe, KOMe, LiOMe, NaOtBu, KOtBu and LiOtBu preferably NaH, or KOtBu or LDA, more preferably in KOtBu in a aprotic solvent selected from the list of DMSO, THF (tetrahydrofuran), DMF (dimethyl formide), NMP (N-methyl pyrrolidon), ethers; such as diethyl ether, methyl tert.butyl ether, ketones; such as acetone, methyl ethyl ketone, methyl isobutyl ketone, hydrocarbons; such as toluene,

benzene, cyclohexane or alkanes and mixtures there of; preferably dimethyl sulfoxide or acetone or toluene, more preferably the solvent is dimethyl sulfoxide, in a anhydrous condition under nitrogen atmosphere, at a temperature of 50 – 120°C; preferably 60-65°C for more than a hour;

(ii) cooling the reaction mixture of step (1) to temperature of 10-50°C, preferably to a temperature of 30-35°C;

(iii) dissolving 5-cyano-1- (4-fluoro phenyl)-1,3-dihydrobenzofuran of formula-VI in a suitable aprotic solvent selected from the list of dimethyl sulfoxide (DMSO), THF (tetrahydrofuran), DMF (dimethyl formide), NMP (N-methyl pyrrolidon), ethers such as diethyl ether, methyl-tert-butyl ether, ketones; such as acetone, methyl ethyl ketone, methyl isobutyl ketone, hydrocarbons such as toluene, benzene, cyclohexane or alkanes and mixtures there of; preferably dimethyl sulfoxide or acetone or toluene, more preferably the solvent is dimethyl sulfoxide, followed by it's addition to the reaction mixture of step (2) at ambient temperature;

(iv) stirring the reaction mass of step (3) for a period of 10 – 60 minutes, preferably for a period of 10-15 minutes;

(v) dissolving the chloropropyl amine of formula-VII in a aprotic solvent selected from the list of dimethyl sulfoxide (DMSO), THF (tetrahydrofuran), DMF (dimethyl formide), NMP (N-methyl pyrrolidon), ethers such as diethyl ether, methyl-tert-butyl ether, ketones; such as acetone, methyl ethyl ketone, methyl isobutyl ketone, hydrocarbons such as toluene, benzene, cyclohexane or alkanes and mixtures there of; preferably dimethyl sulfoxide or acetone or toluene,

more preferably the solvent is dimethyl sulfoxide, followed by addition to the reaction mixture of step (4) at ambient temperature;

(vi) heating the reaction mass of step (5) to a temperature of 40 – 140°C for a period of 1 to 6 hrs; preferably a temperature of 40 – 45°C for 1 to 1.5 hrs;

(vii) quenching of the reaction mass of step (6) using ice- cold water at a temperature of – 5 to 25 °C, preferably at a temperature of 0 to 5°C;

(viii) extraction of the compound from reaction mass of step (7) with an organic solvent selected from the list of dichloromethane, chloroform, dichloroethane, toluene, xylene, ethyl acetate, Isopropyl ether, methyl tert. butyl ether, diethyl ether or petroleum ether, preferably toluene;

(ix) distilling off the solvent under reduced pressure from the reaction solution of step (8) to get the residue;

(x) suspending the residue of step (9) in water followed by adjusting pH of the solution between 2 and 6 with a solution comprising hydrochloric acid, acetic acid, sulphuric acid; preferably hydrochloric acid solution followed by washing solution with a suitable organic solvent selected from class of dichloroethane, chloroform, dichloromethane, toluene, xylene, ethyl acetate, Isopropyl ether, methyl tert. butyl ether, diethyl ether or petroleum ether; preferably toluene;

(xi) basifying the aqueous solution of step (10) to a pH of 8 to 13 with a basic solution comprising of a base such as sodium hydroxide, sodium carbonate sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution;

(xii) extracting the compound from the basified aqueous layer of step (11) with a suitable organic solvent selected from dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with toluene;

(xiii) distilling the solvent from the reaction solution of step (12) to obtain a didesmethylcitalopram of compound of Formula (II) in the form of thick syrup;

(xiv) didesmethylcitalopram of compound of Formula (II) of step (13) optionally purified by converting the free base in to its corresponding acid addition salts in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethyl methyl ketone, methyl isobutyl ketone, chloro solvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene followed by drying to get the acid addition salt of compound of formula (II);

(xv) hydrolysis of the dried or wet salt of formula (II) of the step (14) in water with suitable alkaline solution comprising of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution;

(xvi) extracting the compound of formula (II) from the solution of step (15) in a suitable organic solvent selected from dichloromethane, chloroform, dichloro ethane, toluene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with toluene; and

(xvii) distilling the organic solvent of step (16) to afford the compound of Formula (II) with satisfactory yield and purity.

In the other hand, escitalopram of Formula-I can be prepared by dissolving racemic 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile of Formula (II) in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethyl methyl ketone, methyl isobutyl ketone, chloro solvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile; stirring the reaction mass of step (i) for a period of 5 to 60 minutes, preferably for a period of 10 to 15 minutes; dissolving the enantiomerically pure acid selected from, optically antipodes of tartaric acids such as di-benzoyltartaric acid, di-p-toluyl tartaric acid and o-nitrobenzoyl tartaric acid, lactic acid, bisnaphthylphosphoric acid, camphorsulphonic acid, such as 10 –camphorsulphonic acid and 8 –camphorsulphonic acid, malic acid, N-acetyl glutamic acid, mandelic acid and the like are conveniently used preferably tartaric acid antipodes; more preferably (-) di-p-toluyl tartaric acid in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chloro solvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile at a ambient temperatures; addition of the reaction mass of step (iii) to a reaction mass of step (ii) for a period of 10 to 60 minutes, preferably 10 to 15 minutes; heating the reaction mass of step (iv)

to a temperature of 40 – 100°C for a period of 1 to 6 hours; preferably a temperature of 60 – 65°C for 45to 60 minutes; cooling the reaction mass of step (v) to a temperature of –20 to 10°C for a period of 1 to 3 hours; preferably –5 to 5°C for 1 to 1.5 hours; filtering the obtained solid in step (vi) followed by washing with a solvent used in step (iii); drying the solid obtained in step (vii) at temperature of 40 to 70°C for a period of 2 to 48 hours; preferably at 60 –65°C for 6 to 8 hours to afford a diastereomeric salt of compound of Formula (II); dissolving the diastereomeric salt obtained in step (viii) in a suitable solvent such as water, list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chloro solvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably in a mixture of 15:1 acetonitrile and water combination; heating the reaction mass of step (ix) to a temperature of 40 – 100°C for a period of 1 to 6 hours; preferably a temperature of 60 –65°C for 45 to 60 minutes; cooling the reaction mass of step (x) to a temperature of –20 to +30°C for a period of 1 to 72 hours; preferably –5 to 5°C for 1 to 3 hours; filtering the obtained solid in step (xi) followed by washing with a solvent used in step (ix); drying the solid obtained in step (xii) at temperature of 40 to 70°C for a period of 2 to 48 hours; preferably at 60 –65°C for 6 to 8 hours to afford (+)-1- (3- aminopropyl)-1-(4 – fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile in form of (-) DPTTA salt of compound of Formula (XI); suspending the solid obtained in step (xiii) in water followed by adjusting pH of the solution between 8 to 13 with a base solution comprising of sodium hydroxide, sodium carbonate sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution; extracting the

compound of formula -XI from the basified aqueous layer of step (xiv) with a suitable organic solvent selected from dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with toluene; distilling the solvent from the reaction solution of step (xv) to obtain (+) didesmethylcitalopram of compound of Formula (XI) with satisfactory yield and purity; reacting the compound formula (XI) in step (xvi) with suitable ethylating agents such as methyl iodide, dimethyl soleplate or mixture of formic acid and formaldehyde at a temperature of 20 to 150 °C for 4 to 24 hours, preferably with formic acid and formaldehyde at 80 to 100°C for 10 to 18 hours, more preferably with formic acid and formaldehyde at 95 to 100°C for 12 hours; cooling the reaction mass of step (xvii) to ambient temperature followed by addition of inorganic acid such as hydrochloride acid, sulphuric acid, preferably hydrochloric acid; distilling the reaction solution of step (xviii) to obtain a thick residue; suspending the residue of step (xix) in basic solution comprising of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate, preferably aqueous sodium hydroxide; extracting the compound from the basified aqueous layer of step (xx) with an organic solvent comprising of dichloromethane, chloroform, dichloro ethane, toluene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably diethyl ether; distilling the solvent from the reaction solution of step (xxi) to afford (+)-1-[3 – (N, N'- dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro –5 – isobenzofurancarbonitrile of the Formula – I.

R-citalopram of formula-V can be prepared by;

(i) dissolving racemic 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile of Formula (II) in a suitable solvent selected

from the list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chloro solvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile;

(ii) stirring the reaction mass of step (i) for a period of 5 to 60 minutes, preferably for a period of 10 to 15 minutes;

(iii) dissolving the enantiomerically pure acid selected from, optically antipodes of tartaric acids such as di-benzoyltartaric acid, di-p-toluyl tartaric acid and o-nitrobenzoyl tartaric acid, lactic acid, bisnaphthylphosphoric acid, camphorsulphonic acid, such as 10 –camphorsulphonic acid and 8 – camphorsulphonic acid, malic acid, N-acetyl glutamic acid, mandelic acid and the like are conveniently used preferably tartaric acid antipodes; more preferably (+) di-p-toluyl tartaric acid in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chloro solvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile at a ambient temperatures;

(iv) addition of reaction mass of step (iii) to reaction mass of step (ii) for a period of 10 to 60 minutes, preferably 10 to 15 minutes;

(v) Heating the reaction mass of step (iv) to a temperature of 40 – 100°C for a period of 1 to 6 hours; preferably a temperature of 60 –65°C for 45to 60 minutes;

(vi) Cooling the reaction mass of step (v) to a temperature of –20 to 40°C for a period of 1 to 3 hours; preferably –5 to 5°C for 1 to 1.5 hours;

(vii) filtering the obtained solid in step (vi) followed by its washing with a solvent used in step (ii);

(viii) drying the solid obtained in step (vii) at temperature of 40 to 70°C for a period of 2 to 48 hours; preferably at 60 –65°C for 6 to 8 hours to afford diastereomeric salt of compound of Formula (II);

(ix) dissolving the diastereomeric salt obtained in step (viii) in a suitable solvent such as water, list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethyl methyl ketone, methyl isobutyl ketone, chloro solvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile and water combination at a ambient temperatures;

(x) heating the reaction mass of step (ix) to a temperature of 40 – 100°C for a period of 1 to 6 hours; preferably 60 –65°C for 45 to 60 minutes;

(xi) cooling the reaction mass of step (x) a temperature of –20 to 10°C for a period of 1 to 8 hours; preferably –5 to 5°C for 1 to 3 hours;

(xii) filtering the obtained solid in step (xi) followed by its washing with a solvent used in step (ix);

(xiii) drying the solid obtained in step (xii) at temperature of 40 to 70°C for a period of 2 to 48 hours; preferably at 60 –65°C for 6 to 8 hours to afford a solid of (-)-1- (3-aminopropyl)-1-(4 -fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile in form of (+) DPTTA salt of compound of Formula (XII);

(xiv) suspending the solid obtained in step (xiii) in water followed by adjusting pH of the solution between 8 to 13 with a base solution comprising of sodium hydroxide, sodium carbonate sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution;

(xv) extracting the compound from the basifying aqueous layer of step (xiv) with a suitable organic solvent selected from dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with toluene;

(xvi) distilling the solvent from the reaction solution of step (xv) to obtain (-) didesmethylcitalopram of compound of Formula (XII) with satisfactory yield and purity;

(xvii) reacting the compound formula (XII) in step (xvi) with suitable methylating agents such as methyl iodide, dimethyl sulphate or mixture of formic acid and formaldehyde at a temperature of 20 to 150 °C for 4 to 24 hours, preferably with formic acid and formaldehyde at 80 to 100°C for 10 to 18 hours, more preferably with formic acid and formaldehyde at 95 to 100°C for 12 hours;

(xviii) cooling the reaction mass of step (xvii) to ambient temperature followed by addition of inorganic acid such as hydrochloride acid, sulphuric acid, preferably hydrochloric acid;

(xix) distilling the reaction solution of step (xviii) to obtain a thick residue;

(xx) suspending the residue of step (xix) in basic solution comprising of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate, preferably aqueous sodium hydroxide;

(xxi) extracting the compound from the basified aqueous layer of step (xx) with an organic solvent comprising of dichloromethane, chloroform, dichloro ethane, toluene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably diethyl ether; and

(xxii) distilling the solvent from the reaction solution of step (xxi) to afford (-)-1-[3 – (N, N'- dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro –5 – isobenzofurancarbonitrile of the formula – V.

Citalopram of formula-VIII can be prepared by;

(i) heating a solution of a base selected form, LDA (lithium diisopropyl amine), NaH, n-BuLi, and metal oxides; such as NaOMe, KOMe, LiOMe, NaOtBu, KOtBu and LiOtBu preferably NaH, or KOtBu or LDA, more preferably in KOtBu in a aprotic solvent selected from the list of DMSO, THF (tetrahydrofuran), DMF (dimethyl formide), NMP (N-methyl pyrrolidon), ethers; such as diethyl ether, methyl tert.butyl ether, ketones; such as acetone, methyl ethyl ketone, methyl isobutyl ketone, hydrocarbons; such as toluene, benzene, cyclohexane or alkanes and mixtures there of; preferably dimethyl sulfoxide or acetone or toluene, more preferably the solvent is dimethyl sulfoxide, in a anhydrous condition under nitrogen atmosphere, at a temperature of 50 – 120°C; preferably 60-65°C for more than a hour;

(ii) cooling the reaction mixture of step (i) to temperature of 10-50°c, preferably to a temperature of 30-35°C;

(iii) dissolving 5-cyano-1- (4-fluoro phenyl)-1,3-dihydrobenzofuran of formula-V in a suitable aprotic solvent selected from the list of dimethyl sulfoxide (DMSO), THF (tetrahydrofuran), DMF (dimethyl formide), NMP (N-methyl pyrrolidon), ethers such as diethyl ether, methyl-tert-butyl ether, ketones; such as acetone, methyl ethyl ketone, methyl isobutyl ketone, hydrocarbons such as toluene, benzene, cyclohexane or alkanes and mixtures there of; preferably dimethyl sulfoxide or acetone or toluene, more preferably the solvent is dimethyl sulfoxide, followed by it's addition to the reaction mixture of step (ii) at ambient temperature;

(iv) stirring the reaction mass of step (iii) for a period of 10 – 60 minutes, preferably for a period of 10-15 minutes;

(v) dissolving the chloropropyl amine of formula-VI in a aprotic solvent selected from the list of dimethyl sulfoxide (DMSO), THF (tetrahydrofuran), DMF (dimethyl formide), NMP (N-methyl pyrrolidon), ethers such as diethyl ether, methyl-tert-butyl ether, ketones; such as acetone, methyl ethyl ketone, methyl isobutyl ketone, hydrocarbons such as toluene, benzene, cyclohexane or alkanes and mixtures there of; preferably dimethyl sulfoxide or acetone or toluene, more preferably the solvent is dimethyl sulfoxide, followed by it's addition to the reaction mixture of step (63) at ambient temperature;

(vi) heating the reaction mass of step (v) to a temperature of 40 – 140°C for a period of 1 to 6 hrs; preferably a temperature of 40 – 45°C for 1 to 1.5 hrs;

(vii) quenching of the reaction mass of step (vi) using ice- cold water at a temperature of – 5 to 25 °C, preferably at a temperature of 0 to 5°C;

(viii) extraction of the compound from reaction mass of step (vii) with an organic solvent selected from the list of dichloromethane, chloroform, dichloroethane, toluene, xylene, ethyl acetate, Isopropyl ether, methyl tert. butyl ether, diethyl ether or petroleum ether, preferably toluene;

(ix) distilling off the solvent under vacuum from the reaction solution of step (viii) to get the residue;

(x) suspending the residue of step (ix) in water followed by adjusting pH of the solution between 2 and 6 with a solution comprising hydrochloric acid, acetic acid, sulphuric acid; preferably hydrochloric acid solution followed by washing solution with a suitable organic solvent selected from class of dichloroethane, chloroform, dichloromethane, toluene, xylene, ethyl acetate, Isopropyl ether, methyl tert. butyl ether, diethyl ether or petroleum ether; preferably toluene;

(xi) basifying the aqueous solution of step (x) to a pH of 8- 13 with a base solution comprising of sodium hydroxide, sodium carbonate sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution;

(xii) extracting the compound from the basified aqueous layer of step (xi) with a suitable organic solvent selected from dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with toluene;

(xiii) distilling the solvent from the reaction solution of step (xii) to obtain a didesmethylcitalopram of compound of Formula (II) in the form of thick syrup;

(xiv) which is optionally purified by converting the free base in to its corresponding acid addition salts in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethyl methyl ketone, methyl isobutyl ketone, chloro solvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene followed by drying to get the acid addition salt of compound of formula (II);

(xv) hydrolysis of the dried or wet salt of formula (II) of the step (xiv) in water with suitable alkaline solution comprising of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution;

(xvi) extracting the compound of formula (II) from the solution of step (xv) in a suitable organic solvent selected from dichloromethane, chloroform, dichloro ethane, toluene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with toluene;

(xvii) distilling the organic solvent of step (xvi) to afford the compound of formula (II) with satisfactory yield and purity;

(xviii) reacting the compound formula (II) in step (xvii) with suitable methylating agents such as methyl iodide, dimethyl sulphate or mixture of formic acid and formaldehyde at a temperature of 20 to 150 °C for 4 to 24 hours, preferably with

formic acid and formaldehyde at 80 to 100°C for 10 to 18 hours, more preferably with formic acid and formaldehyde at 95 to 100°C for 12 hours;

(xix) cooling the reaction mass of step (xviii) to ambient temperature followed by addition of inorganic acid such as hydrochloride acid, sulphuric acid, preferably hydrochloric acid;

(xx) distilling the reaction solution of step (xix) to obtain a thick residue;

(xxi) suspending the residue of step (xx) in basic solution comprising of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate, preferably aqueous sodium hydroxide;

(xxii) extracting the compound from the basified aqueous layer of step (xxi) with an organic solvent comprising of dichloromethane, chloroform, dichloro ethane, toluene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably diethyl ether; and

(xxiii) distilling the solvent from the reaction solution of step (xxii) to afford racemic 1-[3 – (N, N'- dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro –5 – isobenzofurancarbonitrile of the Formula – VIII.

Racemic desmethylcitalopram of Formula-XIII can be prepared by

(i) dissolving the didesmethyl citalopram of Formula (II) in a solvent selected from the list of solvents ethers; such as diethyl ether, methyl-tert-butyl ether, hydrocarbons; such as toluene, benzene, cyclohexane or alkanes and mixtures thereof; preferably the solvent is toluene;

(ii) addition of benzaldehyde to reaction mass of step (i) to ambient temperature;

(iii) refluxing the above reaction mass of step (ii) with a water separator for a period of 2 to 10 hours at a temperature of 100-110°C preferably till the last drop of the water was collected;

(iv) reacting the reaction mass of step (iii) with suitable methylating agents such as methyl iodide, dimethyl sulphate or mixture of formic acid and formaldehyde at a temperature of 20 to 150 °C for 1 to 10 hours, preferably with dimethyl sulphate at 100 to 110°C for 1-1.5 hours;

(v) cooling the reaction mass of step (iv) to a temperature of 90-95°C;

(vi) treating the reaction mass of step (v) with water at a temperature at 90-95°C;

(vii) refluxing the reaction mass of step (vi) for a period of 20 –120 minutes at 90-125°C preferably 100-110°C for 30-40 minutes;

(viii) cooling the reaction mass of step (vii) to ambient temperature and followed by washing with a suitable organic solvents selected from the class of dichloroethane, chloroform, dichloromethane, toluene, xylene, ethyl acetate, Isopropyl ether, methyl tert. butyl ether, diethyl ether or petroleum ether; preferably diethyl ether;

(ix) basifying the aqueous solution of step (viii) to a pH of 8- 13 with a base solution comprising of sodium hydroxide, sodium carbonate sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution more preferably to a pH of 12-13;

(x) extracting the compound from the basified aqueous layer of step (ix) with a suitable organic solvents selected from dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with diethyl ether;

(xi) washing the organic layer of step (x) with water followed by its drying with suitable dehydrating agents preferably with anhydrous sodium sulfate;

(xii) distilling the solvent from the reaction solution of step (xi) to obtain a racemic desmethyl citalopram of compound of Formula (XIII) in the form of thick syrup; and

(xiii) which is optionally purified by converting the free base in to its corresponding acid addition salts in a suitable solvent selected from the list of alcohols; such as methanol, ethanol, isopropanol, butanol, ketone such as acetone, ethyl methyl ketone, methyl isobutyl ketone, chloro solvents; such as dichloroethane, dichloromethane, chloroform, esters; such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons; such as toluene, benzene, cyclohexane, heptane, hexanes, xylene followed by drying to get the acid addition salt of compound of Formula (XIII).

(+) Desmethylcitalopram of Formula-IX can be prepared by

(i) dissolving racemic 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile of Formula (II) in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol, ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chloro solvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile;

(ii) stirring the reaction mass of step (i) for a period of 5 to 60 minutes, preferably for a period of 10 to 15 minutes;

(iii) dissolving the enantiomerically pure acid selected from, optically antipodes of tartaric acids such as di-benzoyltartaric acid, di-p-toluyl tartaric acid and o-nitrobenzoyl tartaric

acid, lactic acid, bisnaphthylphosphoric acid, camphorsulphonic acid, such as 10 – camphorsulphonic acid and 8 –camphorsulphonic acid, malic acid, N-acetyl glutamic acid, mandelic acid and the like are conveniently used preferably tartaric acid antipodes; more preferably (-) di-p-toluyl tartaric acid in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chloro solvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile at a ambient temperatures;

(iv) addition of reaction mass of step (iii) to reaction mass of step (ii) for a period of 10 to 60 minutes, preferably 10 to 15 minutes;

(v) heating the reaction mass of step (iv) to a temperature of 40 – 100°C for a period of 1 to 6 hours; preferably a temperature of 60 –65°C for 45 to 60 minutes;

(vi) cooling the reaction mass of step (v) a temperature of –20 to 10°C for a period of 1 to 3 hours; preferably –5 to 5°C for 1 to 1.5 hours;

(vii) filtering the obtained solid in step (vi) followed by its washing with a solvent used in step (i);

(viii) drying the solid obtained in step (vii) at temperature of 40 to 70°C for a period of 2 to 48 hours; preferably at 60 –65°C for 6 to 8 hours to afford a solid of diastereomeric salt of compound of Formula (II);

(ix) dissolving the diastereomeric salt obtained in step (viii) in a suitable solvent such as water, list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such

as acetone, ethyl methyl ketone, methyl isobutyl ketone, chloro solvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile and water combination at a ambient temperatures;

(x) heating the reaction mass of step (ix) to a temperature of 40 to 100°C for a period of 1 to 6 hours; preferably a temperature of 60 to 65°C for 45 to 60 minutes;

(xi) cooling the reaction mass of step (x) a temperature of –20 to 10°C for a period of 1 to 8 hours; preferably –5 to 5°C for 1 to 3 hours;

(xii) filter the obtained solid in step (xi) followed by its washing with a solvent used in step (ix);

(xiii) drying the solid obtained in step (xii) at temperature of 40 to 70°C for a period of 2 to 48 hours; preferably at 60 –65°C for 6 to 8 hours to afford a solid of (+)-1- (3-aminopropyl)-1-(4 -fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile in form of DPTTA salt of compound of Formula (XI);

(xiv) dissolving the solid obtained in step (xiii) in water followed by adjusting pH of the solution between 8 to 13 with a base solution comprising of sodium hydroxide, sodium carbonate sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution;

(xv) extracting the compound from the basifying aqueous layer of step (xiv) with a suitable organic solvent selected from dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with toluene;

(xvi) distilling the solvent from the reaction solution of step (xv) to obtain a compound of formula (+) didesmethylcitalopram of compound of Formula (XI) with satisfactory yield and purity;

(xvii)dissolving the (+)-didesmethyl citalopram of Formula (XI) in a solvents selected from the list of solvents ethers; such as diethyl ether, methyl-tert-butyl ether, hydrocarbons; such as toluene, benzene, cyclohexane or alkanes and mixtures there of; preferably the solvent is toluene;

(xviii) addition of benzaldehyde to reaction mass of step (xvii) at ambient temperatures;

(xix) refluxing the above reaction mass of step (xviii) with a water separator for a period of 2 to 10hrs at a temperature of 100-110°C preferably till the last drop of the water was collected;

(xx) reacting the reaction mass of step (xix) with suitable methylating agents such as methyl iodide, dimethyl sulphate or mixture of formic acid and formaldehyde at a temperature of 20 to 150 °C for 1 to 10 hours, preferably with dimethyl sulphate at 100 to 110°C for 1 to 1.5 hours;

(xxi) cooling the reaction mass of step (xx) to a temperature of 90-95°C;

(xxii) treating the reaction mass of step (xxi) with water at a temperature at 90-95°C;

(xxiii) refluxing the reaction mass of step (xxii) for a period of 20 –120 minutes at 90-125°C preferably 100-110°C for 30-40 minutes;

(xxiv) cooling the reaction mass of step (xxiii) to ambient temperature and followed by washing with a suitable organic solvents selected from the class of dichloroethane,

chloroform, dichloromethane, toluene, xylene, ethyl acetate, Isopropyl ether, methyl tert. butyl ether, diethyl ether or petroleum ether; preferably diethyl ether;

(xxv) basifying the aqueous solution of step (xxiv) to a pH of 8- 13 with a base solution comprising of sodium hydroxide, sodium carbonate sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution more preferably to a pH of 12-13;

(xxvi) extracting the compound from the basified aqueous layer of step (xxv) with a suitable organic solvents selected from dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with diethyl ether;

(xxvii) washing the organic layer of step (xxvi) with water followed by its drying with suitable dehydrating agents preferably with anhydrous sodium sulfate;

(xxviii)distilling the solvent from the reaction solution of step (xxvii) to obtain a (+)-desmethyl citalopram of compound of Formula (IX) in the form of thick syrup; and

(xxix) which is optionally purified by converting the free base in to its corresponding acid addition salts in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol, ketone such as acetone, ethyl methyl ketone, methyl isobutyl ketone, chloro solvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene followed by drying to get the acid addition salt of compound of formula (IX).

(-) - Desmethylcitalopram of formula-X can be prepared by

(i) dissolving racemic 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile of Formula (II) in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chloro solvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile;

(ii) stirring the reaction mass of step (i) for a period of 5 to 60 minutes, preferably for a period of 10 to 15 minutes;

(iii) dissolving the enantiomerically pure acid selected from, optically antipodes of tartaric acids such as di-benzoyltartaric acid, di-p-toluyl tartaric acid and o-nitrobenzoyl tartaric acid, lactic acid, bisnaphthylphosphoric acid, camphorsulphonic acid, such as 10 –camphorsulphonic acid and 8 – camphorsulphonic acid, malic acid, N-acetyl glutamic acid, mandelic acid and the like are conveniently used preferably tartaric acid antipodes; more preferably (+) di-p-toluyl tartaric acid in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chloro solvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile at a ambient temperatures;

(iv) addition of reaction mass of step (iii) to reaction mass of step (ii) for a period of 10 to 60 minutes, preferably 10 to 15 minutes;

(v) heating the reaction mass of step (iv) to a temperature of 40 – 100°C for a period of 1 to 6 hours; preferably a temperature of 60 –65°C for 45to 60 minutes;

(vi) cooling the reaction mass of step (v) a temperature of –20 to 10°C for a period of 1 to 3 hours; preferably –5 to 5°C for 1 to 1.5 hours;

(vii) Filter the obtained solid in step (vi) followed by its washing with a solvent used in step (i);

(viii) drying the solid obtained in step (vii) at temperature of 40 to 70°C for a period of 2 to 48 hours; preferably at 60 to 65°C for 6 to 8 hours to afford a diastereomeric salt of compound of Formula (II);

(ix) dissolving the diastereomeric salt obtained in step (viii) in a suitable solvent such as water, list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chloro solvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene or alkanes and mixture thereof; preferably acetonitrile and water combination at a ambient temperatures;

(x) heating the reaction mass of step (ix) to a temperature of 40 – 100°C for a period of 1 to 6 hours; preferably a temperature of 60 –65°C for 45to 60 minutes;

(xi) cooling the reaction mass of step (x) a temperature of –20 to 10°C for a period of 1 to 8 hours; preferably –5 to 5°C for 1 to 3 hours;

(xii) filter the obtained solid in step (xi) followed by its washing with a solvent used in step (ix);

(xiii) drying the solid obtained in step (xii) at temperature of 40 to 70°C for a period of 2 to 48 hours; preferably at 60 –65°C for 6 to 8 hours to afford a solid of (-)-1- (3-aminopropyl)-1-(4 -fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile in form of DPTTA salt of compound of Formula (XII);

(xiv) dissolving the solid obtained in step (139) in water followed by adjusting pH of the solution between 8 to 13 with a base solution comprising of sodium hydroxide, sodium carbonate sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution preferably 12-13;

(xv) extracting the compound from the basifying aqueous layer of step (140) with a suitable organic solvent selected from dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with toluene;

(xvi) distilling the solvent from the reaction solution of step (xv) to obtain a compound of formula (-) didesmethylcitalopram of compound of Formula (XII) with satisfactory yield and purity;

(xvii) dissolving the (-)-didesmethyl citalopram of Formula (XII) in a solvents selected from the list of solvents ethers; such as diethyl ether, methyl-tert-butyl ether, hydrocarbons; such as toluene, benzene, cyclohexane or alkanes and mixtures thereof; preferably the solvent is toluene;

(xviii) addition of benzaldehyde to reaction mass of step (xvii) at ambient temperature;

(xix) refluxing the above reaction mass of step (xviii) with a water separator for a period of 2 to 10 hours at a temperature of 100-110°C preferably till the last drop of the water was collected;

(xx) reacting the reaction mass of step (xix) with suitable methylating agents such as methyl iodide, dimethyl sulphate or mixture of formic acid and formaldehyde at a temperature of 20 to 150 °C for 1 to 10 hours, preferably with dimethyl sulphate at 100 to 110°C for 1-1.5 hours;

(xxi) cooling the reaction mass of step (xx) to a temperature of 90-95°C;

(xxii) treating the reaction mass of step (xxi) with water at a temperature at 90-95°C;

(xxiii) refluxing the reaction mass of step (xxii) for a period of 20 to120 minutes at 90 to125°C preferably 100-110°C for 30-40 minutes;

(xxiv) cooling the reaction mass of step (xxiii) to ambient temperature and followed by washing with a suitable organic solvents selected from the class of dichloroethane, chloroform, dichloromethane, toluene, xylene, ethyl acetate, Isopropyl ether, methyl tert. butyl ether, diethyl ether or petroleum ether; preferably diethyl ether;

(xxv) basifying the aqueous solution of step (xxiv) to a pH of 8- 13 with a base solution comprising of sodium hydroxide, sodium carbonate sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution more preferably to a pH of 12-13;

(xxvi) extracting the compound from the basified aqueous layer of step (xxv) with a suitable organic solvents selected from dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with diethyl ether;

(xxvii) washing the organic layer of step- (xxvi) with water followed by its drying with suitable dehydrating agents preferably with anhydrous sodium sulfate;

(xxviii) distilling the solvent from the reaction solution of step (xxvii) to obtain a (-)-desmethyl citalopram of compound of Formula (X) in the form of thick syrup; and

(xxix) which is optionally purified by converting the free base in to its corresponding acid addition salts in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol, ketone such as acetone, ethyl methyl ketone, methyl isobutyl ketone, chloro solvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene followed by drying to get the acid addition salt of compound of formula (X).

The following examples are only illustrative and are not intended to limit the scope of the invention in any way whatsoever.

Example-1

Preparation of 1- (3- aminopropyl)-1-(4 -fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile (Formula-II)

A potassium salt of DMSO was prepared by adding 7.5 gm of potassium tertiary butoxide in DMSO (40 ml) at 60-65°C under nitrogen atmosphere. To the resulting solution a solution of 1-(4-fluorophenyl)-1,3-dihydroiso benzofuran-5-carbonitrile (10gm) in DMSO (35 ml) was added within 10 minutes at 25 –30 °C. After maintaining for 15-20 minutes, a solution of 3-chloropropyl amine (12gm) in DMSO (2.5ml) was added at once at the temperature between 25-30°C. After the addition is over, reaction mixture was heated slowly to 40-45°C for 60 to 70 minutes. The reaction mixture is then quenched with ice-cold water (200 ml) and

extracted with toluene (100 ml). Aq. Layer was again extracted with (3 x 100 ml) of toluene. Toluene layer was dried over anhydrous sodium sulphate and distilled off under vacuum below 65°C to get thick syrup. Then resulting residue was suspended in 50 ml water and acidified to a pH 2-3 with 10% aqueous Hydrochloric acid solution. The resulting acidic solution was then washed with (4 x 100 ml) of toluene. The aq layer was basified with 10% aqueous sodium hydroxide solution to pH 10-11and extracted with (3 x 100 ml) of toluene. The combined toluene layer was washed with water (2 x 100 ml), followed by distillation of toluene layer to afford the compound of the formula (V) as wine red syrup (10 gm).

Example-2 (In Acetone)

Preparation of 1- (3- aminopropyl)-1-(4 -fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile (Formula-II)

A potassium salt of DMSO was prepared by adding 7.5 gm of potassium tertiary butoxide in acetone (40 ml) at 60-65°C under nitrogen atmosphere. To the resulting solution a solution of 1-(4-fluorophenyl)-1,3-dihydroiso benzofuran-5-carbonitrile (10gm) in acetone (35 ml) was added within 10 minutes at 25 –30 °C. After maintaining for 15-20 minutes, a solution of 3-chloropropyl amine (12 gm) in acetone (2.5ml) was added at once at the temperature between 25-30°C. After the addition is over, reaction mixture was heated slowly to 40-45°C for 60 to 70 minutes. The reaction mixture is then quenched with ice-cold water (200 ml) and extracted with toluene (100 ml). Aq. Layer was again extracted with (3 x 100 ml) of toluene. Toluene layer was dried over anhydrous sodium sulphate and distilled off under vacuum below 65°C to get thick syrup. Then resulting residue was suspended in 50 ml water and acidified to a pH 2-3 with 10% aqueous Hydrochloric acid solution. The resulting acidic solution was then washed with (4 x 100 ml) of toluene. The aqueous layer was basified with 10% aqueous

sodium hydroxide solution to pH 10-11and extracted with (3 x 100 ml) of toluene. The combined toluene layer was washed with water (2 x 100 ml), followed by distillation of toluene layer to afford the compound of the formula (V) as wine red syrup (8 gm).

Example-3

Preparation of (+)-1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3–dihydro-iso benzofuran – 5 – carbonitrile: (Formula-XI)

1-(3- aminopropyl)-1-(4 -fluorophenyl)-1,3 dihydroisobenzofuran – 5 – carbonitrile (10 gm) was dissolved in 50 ml of acetonitrile. A solution of (-)-di-p-tolyltartaric acid (13 gm in 20 ml of acetonitrile) was added slowly at ambient temperature. The reaction mixture was stirred at ambient temperature to obtain thick solid. The reaction mixture was heated to 60 –65°Cfor 45 to 60 minutes and the resulting the reaction mass was cooled to 0-5°C. The reaction mass was stirred at 0-5°C for the period of 1 hour and resulting solid was filtered under vacuum. Further the wet solid was dried at 60-65°C for the period of 6 to8 hours. The resulting solid was suspended in 150ml of acetonitrile and heated to reflux. 10 ml of DM water was added under reflux to obtain a clear solution. The reaction mixture was cooled to 0-5°C for 3 hours. Thus precipitated solid was filtered off and suspended in 100 ml of water. pH of the suspension was adjusted to 12 and then extracted with (3 x 100 ml) of toluene. Combined toluene layers was washed with water (2 x 50 ml), dried over anhydrous sodium sulphate, followed by distillation to afford (+)-1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3–dihydro-iso benzofuran – 5 – carbonitrile as an syrup (3.0 gm).

$[\alpha]^{25}_{D}$ = (+) 12.04° (C=1%in methanol), Chiral purity by HPLC=98.32%

Example-4

Preparation of (-) 1- (3 - aminopropyl) 1-(4 -fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile: (Formula-XII)

1-(3- aminopropyl)-1-(4 -fluorophenyl)-1,3 dihydroisobenzofuran – 5 – carbonitrile (10 gm) was dissolved in 50 ml of acetonitrile. A solution of (+)-di-p-tolyltartaric acid (13 gm in 20 ml of acetonitrile) was added slowly at ambient temperature. The reaction mixture was stirred at ambient temperature to obtain thick solid. The reaction mixture was heated to 60 – 65°Cfor 45 to 60 minutes and the resulting the reaction mass was cooled to 0-5°C. The reaction mass was stirred at 0-5°C for the period of 1 hour and resulting solid was filtered under vacuum. Further the wet solid was dried at 60-65°C for the period of 6 to8 hours. The resulting solid was suspended in 150ml of acetonitrile and heated to reflux. 10 ml of DM water was added under reflux to obtain a clear solution. The reaction mixture was cooled to 0-5°C for 3 hours. Thus precipitated solid was filtered off and suspended in 100 ml of water. pH of the suspension was adjusted to 12 and then extracted with (3 x 100 ml) of toluene. Combined toluene layers was washed with water (2 x 50 ml), dried over anhydrous sodium sulphate, followed by distillation to afford (-)-1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3–dihydro-iso benzofuran – 5 – carbonitrile as an syrup (2.8 gm).

$[\alpha]^{25}_{D}$ =(-)12.07°(C=1%in methanol), Chiral purity by HPLC=98.61%

Example-5

Preparation of (+) 1- (3 - dimethylaminopropyl) 1-(4 -fluorophenyl)-1,3 – dihydroisobenzofuran – 5 – carbonitrile: (Formula-I)

A solution of (+) 1-(3- aminopropyl)-1-(4 -fluorophenyl)-1,3 dihydroisobenzofuran – 5 – carbonitrile (5 gm, 0.017 mole) and formaldehyde (2.5 gm, 0.084 mole, 37% aqueous

solution) in 98 % formic acid (3.88 gm, 0.084 mole) was refluxed at 95 – 100°C for the 12 hours. After the solution has been cooled 5 ml of 4 N Hydrochloric acid solutions was added and resulting reaction solution is evaporated to dryness under reduced pressure. Then 1 N sodium hydroxide solution (100ml) was added to the residue and extracted with diethyl ether (3 x 100 ml). The organic extract was washed with water (2 x 100 ml), dried over anhydrous sodium sulphate and distilled off to afford the compound of the formula – I in the form of syrup (4.2 gm).

$[\alpha]^{25}_{D}$ =(+)11.26° (C=1%in methanol), Chiral purity by HPLC=97.05%

Example-6

Preparation of (-) 1- (3 - dimethylaminopropyl) 1-(4 -fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile: (Formula-V)

A solution of (-) 1-(3- aminopropyl)-1-(4 -fluorophenyl)-1,3 dihydroisobenzofuran – 5 – carbonitrile (5 gm, 0.017 mole) and formaldehyde (2.5 gm, 0.084 mole, 37% aqueous solution) in 98 % formic acid (3.88 gm, 0.084 mole) was refluxed at 95 – 100°C for the 12 hours. After the solution has been cooled 5 ml of 4 N Hydrochloric acid solutions was added and resulting reaction solution is evaporated to dryness under reduced pressure. Then 1 N sodium hydroxide solution (100ml) was added to the residue and extracted with diethyl ether (3 x 100 ml). The organic extract was washed with water (2 x 100 ml), dried over anhydrous sodium sulphate and distilled off to afford the compound R-citalopram in the form of syrup (4.3gm).

$[\alpha]^{25}_{D}$ =(-)12.30° (C=1%in methanol), Chiral purity by HPLC=98.05%

Example-7

Preparation of 1- (3 - dimethylaminopropyl) 1-(4 -fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile: (Formula-VIII)

A solution of 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3 dihydro-iso benzofuran – 5 – carbonitrile (5 gm, 0.017 mole) and formaldehyde (2.5 gm, 0.084 mole, 37% aqueous solution) in 98 % formic acid (3.88 gm, 0.084 mole) was refluxed at 95 – 100°C for the 12 hours. After the solution has been cooled 5 ml of 4 N Hydrochloric acid solutions was added and resulting reaction solution is evaporated to dryness under reduced pressure. Then 1 N sodium hydroxide solution (100ml) was added to the residue and extracted with diethyl ether (3 x 100 ml). The organic extract was washed with water (2 x 100 ml), dried over anhydrous sodium sulphate and distilled off to afford the compound citalopram in the form of syrup (4.1 gm).

Example-8

Preparation of 1- (3 – methylaminopropyl) 1-(4 -fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile: (Formula-XIII)

10 gm of 1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3 dihydro-iso benzofuran – 5 – carbonitrile (0.033 mole) and benzaldehyde (4.2gm, 0.040 mole) were refluxed in a water separator for 1.5 – 2.0 hrs. in 20 ml of toluene. To the resulting solution was added 5.1 gm dimethyl sulphate (0.0405 mole) in 20 ml toluene at such a rate as to maintain reflux (15 min.). The reaction mixture was refluxed for 90 minutes, cooled and slowly treated with 30 ml water and heated to reflux for an additional 20 minutes. Cool the reaction mass and separated the aq. layer. The aq. layer was washed twice with 2 x 15 ml of diethyl ether to remove unreacted benzaldehyde and made basic pH 12 –13 with 50 % aq. NaOH. This basic aq. layer was extracted with 2 x 30 ml of diethyl ether. The organic extract was washed with water (2 x 10

ml), dried over anhydrous sodium sulphate and distilled off to afford 8 gm of the compound desmethyl citalopram in the form of syrup. The oxalate salt of the desmethyl citalopram crystallized from acetone. (8.0gm)

Example-9

Preparation of (+)-1- (3 – methylaminopropyl) 1-(4 -fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile: (Formula-IX)

10 gm of (+)-1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3 dihydro-iso benzofuran – 5 – carbonitrile (0.033 mole) and benzaldehyde (4.2gm, 0.040 mole) were refluxed in a water separator for 1.5 – 2.0 hrs. in 20 ml of toluene. To the resulting solution was added 5.1 gm dimethyl sulphate (0.0405 mole) in 20 ml toluene at such a rate as to maintain reflux (15 min.). The reaction mixture was refluxed for 50 minutes, cooled and slowly treated with 30 ml water and hated for an additional 20 minutes. After cooling in ice, the aq. layer was washed twice with 2 x 15 ml of diethyl ether to remove unreacted benzaldehyde and made basic pH 12 –13 with 50 % aq. NaOH. This basic aq. layer was extracted with 2 x 30 ml of diethyl ether. The organic extract was washed with water (2 x 10 ml), dried over anhydrous sodium sulphate and distilled off to afford 7 gm of the compound (+)-desmethyl citalopram in the form of oil. The oxalate salt of the (+)-desmethyl citalopram crystallized from acetone.

$[\propto]^{25}_{D}$ =(+)9.8° (C=1%in methanol),

Example-10

Preparation of (-)-1- (3 – methylaminopropyl) 1-(4 -fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile: (Formula-X)

10 gm of (-)-1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3 dihydro-iso benzofuran – 5 – carbonitrile (0.033 mole) and benzaldehyde (4.2gm, 0.040 mole) were refluxed in a water

separator for 1.5 – 2.0 hrs. in 20 ml of toluene. To the resulting solution was added 5.1 gm dimethyl sulphate (0.0405 mole) in 20 ml toluene at such a rate as to maintain reflux (15 min.). The reaction mixture was refluxed for 50 minutes, cooled and slowly treated with 30 ml water and hated for an additional 20 minutes. After cooling in ice, the aq. layer was washed twice with 2 x 15 ml of diethyl ether to remove unreacted benzaldehyde and made basic pH 12 –13 with 50 % aq. NaOH. This basic aq. layer was extracted with 2 x 30 ml of diethyl ether. The organic extract was washed with water (2 x 10 ml), dried over anhydrous sodium sulphate and distilled off to afford 8.2 gm of the compound (-)-desmethyl citalopram in the form of oil. The oxalate salt of the (-)-desmethyl citalopram crystallized from acetone.

Example 11 (Alternative process for the preparation of Escitalopram)

Preparation of (+) 1- (3 - dimethylaminopropyl) 1-(4 -fluorophenyl)-1,3 – dihydroisobenzofuran – 5 – carbonitrile: (Formula-I)

Racemic 1-(3-dimethylaminopropyl)-1-(4-flourophenyl)-1,3dihydroisobenzo furan -5-carbonitrile (50gm), (+)-di-p-tolyltartaricacid (62gm) were suspended in 500 ml acetonitrile. The reaction mixture was stirred at ambient temperature for a period of 10-15 minutes. Further the contents were heated to 70-75°C, methanol (40.0ml) was added to the same, till a clear solution was attained. The resulting reaction mass was stirred at same temperatures for a period of 30-45 minutes. Then the reaction mass was cooled to 30 –35°C for a period of 2- 3 hours and resulting solid was filtered under vacuum. The obtained filtrate was evaporated to dryness and the resultant thick residue was suspended in aqueous sodium hydroxide solution (1.6g NaOH in 100ml Dm water). To the reaction solution toluene (100ml) was added. The reaction mixture was stirred for a period of 30-45mins, toluene layer was separated and aqueous basic solution was extracted with toluene (3 x 20ml) combined toluene layers was washed with water

(3 x 20 ml), separated toluene layer followed by distillation to afford (+) 1- (3 - dimethylaminopropyl) 1-(4 -fluorophenyl)-1,3 –dihydroisobenzofuran – 5 – carbonitrile as an thick syrup (12.0gm). Thus the obtained thick syrup was resubjected to the above process to improve the chiral purity. $[\propto]^{25}_{D}$ =(+)10.8° (C=1%in methanol), Chiral purity by HPLC=98.89%

We Claim

1) A process for the preparation of didesmethylcitalopram (1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile, comprising;

a) heating a solution of a base selected form, LDA (lithium diisopropyl amine), NaH, n-BuLi, and metal oxides; such as NaOMe, KOMe, LiOMe, NaOtBu, KOtBu and LiOtBu preferably NaH, or KOtBu or LDA, more preferably in KOtBu in a aprotic solvent selected from the list of DMSO, THF (tetrahydrofuran), DMF (dimethyl formide), NMP (N-methyl pyrrolidon), ethers; such as diethyl ether, methyl tert.butyl ether, ketones; such as acetone, methyl ethyl ketone, methyl isobutyl ketone, hydrocarbons; such as toluene, benzene, cyclohexane or alkanes and mixtures there of; preferably dimethyl sulfoxide or acetone or toluene, more preferably the solvent is dimethyl sulfoxide, in a anhydrous condition under nitrogen atmosphere, at a temperature of 50 – 120°C; preferably 60-65°C for more than a hour;

b) cooling the reaction mixture of step (a) to temperature of 10-50°C, preferably to a temperature of 25-35°C;

c) dissolving 5-cyano-1- (4-fluoro phenyl)-1,3-dihydrobenzofuran in a suitable aprotic solvent selected from the list of dimethyl sulfoxide, dimethyl formide, N-methyl pyrrolidon, ethers; such as diethyl ether, methyl-tert-butyl ether, ketones; such as acetone, methyl ethyl ketone, methyl isobutyl ketone, hydrocarbons; such as toluene, benzene, cyclohexane or alkanes and mixtures thereof; preferably dimethyl sulfoxide or acetone, more preferably the solvent is dimethyl sulfoxide, followed by its addition to the reaction mixture of step (b) at ambient temperature;

d) stirring the reaction mass of step (c) for a period of 10 to 60 minutes, preferably for a period of 10-15 minutes;

e) dissolving the chloropropyl amine in a aprotic solvent selected from the list of dimethyl sulfoxide, tetrahydrofuran, dimethyl formide, N-methyl pyrrolidon, ethers; such as diethyl ether, methyl-tert-butyl ether, ketones; such as acetone, methyl ethyl ketone, methyl isobutyl ketone, hydrocarbons; such as toluene, benzene, cyclohexane or alkanes and mixtures thereof; preferably dimethyl sulfoxide or acetone, more preferably the solvent is dimethyl sulfoxide, followed by its addition to the reaction mixture of step (d) at ambient temperature;

f) heating the reaction mass of step (e) to a temperature of 40 to 140°C for a period of 1 to 6 hrs; preferably a temperature of 40 to 45°C for 1 to 1.5 hrs;

g) quenching of the reaction mass of step (f) using ice- cold water at a temperature of – 5 to 25 °C, preferably at a temperature of 0 to 5°C;

h) extraction of the compound from reaction mass of step (g) with an organic solvent selected from the list of dichloromethane, chloroform, dichloroethane, toluene, xylene, ethyl acetate, Isopropyl ether, methyl tert. butyl ether, diethyl ether or petroleum ether, preferably toluene;

i) distilling off the solvent under vacuum from the reaction solution of step (h) to get the residue;

j) suspending the residue of step (i) in water followed by adjusting pH of the solution between 2 and 6 with a solution comprising hydrochloric acid, acetic acid, sulphuric acid; preferably hydrochloric acid solution followed by washing solution with a suitable organic solvent selected from class of dichloroethane, chloroform, dichloromethane, toluene,

xylene, ethyl acetate, Isopropyl ether, methyl tert. butyl ether, diethyl ether or petroleum ether; preferably toluene;

k) basifying the aqueous solution of step (j) to a pH of 8 to 13 with a base solution comprising of sodium hydroxide, sodium carbonate sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution;

l) extracting the compound from the basified aqueous layer of step (k) with a suitable organic solvent selected from dichloromethane, chloroform, dichloro ethane, toluene, xylene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with toluene;

m) distilling the solvent from the reaction solution of step (l) to obtain a didesmethylcitalopram(1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile) in the form of syrup;

n) which is optionally purified by converting the free base in to its corresponding acid addition salts in a suitable solvent selected from the list of alcohols, such as methanol, ethanol, isopropanol, butanol or ketone such as acetone, ethylmethyl ketone, methyl isobutyl ketone, chloro solvents such as dichloroethane, dichloromethane, chloroform, esters such as ethyl acetate, nitriles such as acetonitrile, hydrocarbons such as toluene, benzene, cyclohexane, heptane, hexanes, xylene followed by drying to get the acid addition salt of compound didesmethylcitalopram(1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile);

o) hydrolysis of the dried or wet salt of didesmethylcitalopram(1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile) of the step (n) in water with

suitable alkaline solution comprising of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate; preferably using sodium hydroxide solution;

p) extracting the compound of didesmethylcitalopram(1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile) from the solution of step (o) in a suitable organic solvent selected from dichloromethane, chloroform, dichloro ethane, toluene, ethyl acetate, isopropyl ether, methyl tert. butyl ether, diethyl ether and petroleum ether; preferably with toluene; and

q) distilling the organic solvent of step (p) to afford the compound didesmethylcitalopram(1-(3-aminopropyl)-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile).

ABSTRACT

The present invention relates to a process for preparing enantiomerically enriched citalopram via methylating enantiomerically enriched didesmethylcitalopram, which is prepared by directly resolving racemic didesmethylcitalopram using a chiral acid.

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